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Platelet-Activating Factor-Like Lipids Mediate Endothelial Cell Apoptosis Induced by Hypercholesterolemic Low-Density Lipoprotein

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Background: Atherosclerosis is an inflammatory disease and platelet-activating factor (PAF)-like lipids are potent proinflammatory factors. However, their role in the apoptosis of vascular endothelial cells (EC), an important step in atherosclerosis, has not been identified. We recently demonstrated that L5, the most electronegative and a mildly oxidized subfraction of LDL isolated from hypercholesterolemic human plasma, induces apoptosis in cultured EC. **Methods:** We tested the mediator role of PAF-like lipids in L5-induced apoptosis. As a reference, the effects of L5 were compared with those of well-characterized copper-oxidized LDL (oxLDL). **Results:** In bovine aortic EC cultures, both L5 (50 µg/mL) and oxLDL (50 µg/mL) inhibited fibroblast growth factor 2 (FGF2) transcription and Akt phosphorylation. Concomitantly monitored Bcl-2 family proteins revealed reduction in Bcl-2/Bax ratios, partly explaining ensuing apoptosis. FGF2 overexpression preserved Akt phosphorylation and prevented the Bcl-2-dependent apoptosis. WEB-2086 is an antagonist for the G_i-coupled PAF receptor (PAFR) or PAFR-like receptors. WEB-2086 (10 µM) or G_i deactivator pertussis toxin (100 ng/mL) effectively attenuated FGF2 downregulation and the associated apoptosis in cells exposed to either L5 or oxLDL. Phospholipids isolated from oxLDL also induced apoptosis by downregulating FGF2. Pretreating L5 and oxLDL-derived phospholipids with a recombinant PAF acetylhydrolase, a phospholipase A2 that specifically hydrolyzes the short-chain acetyl group at the sn-2 site of PAF-like phospholipids, abolished their effects. In contrast, pretreating L5 and oxLDL-derived phospholipids with phospholipase A1 had no influence on their effects. **Conclusion:** Our findings indicate that PAF-like lipids mediate the apoptotic signal of L5 circulating in patients with hypercholesterolemia. OxLDL mimics L5 functionally because its signal is mediated by similar mediators.

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The Modification of Epitopes on Low Density Lipoprotein by Homocysteine May Affect the Affinity of LDL to LDL Receptors

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Background: ApoB-100 is the only lipoprotein component in low density lipoprotein (LDL). The intravascular metabolism of apoB-100 remains unclear. The increase of LDL in plasma and hyperhomocysteinemia are the important cardiovascular risk factors. A tiny amount of homocysteine in serum automatically circularizes and changes into a chemical group linking to the free radical, homocysteine thioleone (HCTL). **Objectives:** Our project focuses on the change of the immunoreactivity of different epitopes on homocysteine modified LDL which could be recognized by LDL monoclonal antibodies (mAb) in vitro. **Methods:** We obtained plasma LDL from healthy volunteers and separate the extracted LDL into two parts (LDL modified by HCTL and unmodified LDL). Eighteen fine mapped monoclonal antibodies are employed to detect the altered immunoreactivity of homocysteine modified LDL by RIA assay. **Results:** We found that the immunoreactivity of 3 amino acid epitopes on homocysteine modified LDL (2D8: 1438-1481, 3F5: 2835-2922 and 4G3: 2980-3084 amino acid sequences respectively) were conspicuously declined as recognized by respective monoclonal antibodies. Interestingly, the epitopes of 3F5 and 4G3 are situated near or within the LDL receptor binding domain of apoB-100. **Conclusion:** The declinations within 3F5 and 4G3 epitopes might have physiological and pathological significance in that the declinations alter the affinity of modified LDL to LDL-receptors, therefore, increase the affinity to scavenger receptors and initiate the atherosclerosis process.

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Mediterranean and Low Fat Diets Are Associated With Similar Lipid Levels at 12 Months in Patients With Coronary Heart Disease on Statin Therapy

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Background: A low fat diet is recommended for patients with coronary heart disease (CHD). A high fat mediterranean diet, rich in monounsaturates (MUFA) is associated with low CHD rates and is as effective as Low Fat in lowering cholesterol. Long-term relative efficacy of diets for patients on statins is unknown. This study compared Low Fat to Mediterranean diets on lipids and lipoproteins in patients with CHD on standard therapy (including statins).

Method: 68 patients with angiographic CHD were randomised to Low Fat (fat 20-25 % of Energy, saturated fat 8-10 % energy) or Mediterranean (fat 35-40 % energy, > 50% of fat as MUFA). Lipids were measured prior to drug therapy, at randomisation and at 3 and 12 months.

Results: At randomisation and 12 months, 86 % Low Fat patients and 80 % Mediterranean patients were on statins. Similarly, 80% Low Fat and 85 % Mediterranean patients were taking aspirin. Mean fat intake in Low Fat diet was 20% of total energy (SFA 8.5 % of total energy) compared to Mediterranean diet with fat 34% of total energy (57 % of fat as MUFA).

Conclusions: Mediterranean and Low Fat diets are associated with similar lipid and lipoprotein levels at one year in patients with CHD on standard therapy. Recommendations for CHD patients ought to consider a Mediterranean diet as an alternative to Low Fat.

	Low Fat & Mediterranean Pre Statin	Low Fat n = 34			Mediterranean n = 35		
		Week 0	Week 3	Week 12	Week 0	Week 3	Week 12
		Month	Month	Month	Month	Month	Month
Cholesterol	6.59	4.48	4.44	4.42	4.43	4.34	4.52
Triglycerides	2.81	1.59	1.63	1.56	1.48	1.38	1.48
HDL-Cholesterol	1.18	1.11	1.17	1.21	1.17	1.2	1.24
LDL-Cholesterol	3.92	2.61	2.51	2.52	2.58	2.46	2.62

POSTER SESSION

1057 Dietary Therapy and Prevention

Sunday, March 30, 2003, 3:00 p.m.-5:00 p.m.

McCormick Place, Hall A

Presentation Hour: 4:00 p.m.-5:00 p.m.

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Theaflavin-Enriched Green Tea Extract Lowers Low-Density Lipoprotein Cholesterol

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Background: Epidemiologic studies suggest that drinking multiple cups of tea per day lowers low-density lipoprotein cholesterol (LDL), but previous trials of tea drinking and administration of green tea extract have failed to show any impact on lipids and lipoproteins in humans. Theaflavins are formed when green tea is fermented to produce black tea, and animal studies show that green tea catechins and black tea polyphenols increase fecal excretion of fat and cholesterol. **Hypothesis:** A green tea extract enriched with theaflavins will have a favorable effect on the lipid profile of subjects with mild to moderate hypercholesterolemia. **Methods:** A double-blind, randomized, placebo-controlled, parallel-group trial involving 240 men and women age 18 years or older on a low fat diet with baseline LDL between 130-190 mg/dL in 6 outpatient clinics in China. Subjects were given a daily capsule containing theaflavin-enriched green tea extract (375 mg) or placebo for 12 weeks. **Results:** Mean levels (±SEM) of total cholesterol, LDL, high density lipoprotein cholesterol (HDL), and triglycerides changed by -11.3 ± 0.9% (P=0.01), -16.4 ± 1.1% (P=0.01), +2.3 ± 2.1% (P=NS), and +2.6 ± 3.5% (P=NS) respectively in the tea extract group. Mean levels of total cholesterol, LDL, HDL, and triglycerides did not change significantly in the placebo group. No significant adverse events were observed. **Conclusions:** Theaflavin-enriched green tea extract is an effective adjunct to a low fat diet to lower LDL in hypercholesterolemic adults and is well tolerated.

1057-147

Effects of a Carbohydrate-Restricted Diet Versus a Fat- and Calorie-Restricted Diet on Lipid Subfractions

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Introduction: Low carbohydrate (Low Carb) diets have recently gained popularity. While preliminary data suggest no adverse effect of a Low Carb diet on standard serum lipid levels, there is concern that such diets may adversely shift lipid subfractions to a more atherogenic profile relative to a fat- and calorie-restricted (Low Fat) diet. We randomized 80 subjects with severe obesity and a high prevalence (79%) of diabetes or metabolic syndrome to a Low Carb versus a Low Fat diet, and assessed the effects on lipid subfractions known to increase risk of coronary artery disease (CAD) (small dense low density lipoprotein (LDL) cholesterol particles and large very low density lipoprotein (VLDL) particles), as well as effects on large high density lipoprotein (HDL) cholesterol particles which have been shown to be protective against CAD.

Methods: After randomization, subjects received intensive instruction on a Low Carb versus a Low Fat diet. Lipid particle sizes were measured using nuclear magnetic resonance spectroscopy at 6 months, from which concentrations (expressed in medians (interquartile range)) of lipid subfractions were derived.

Results: Low Carb group subjects experienced a greater decrease in large VLDL (from 46 (15,79) mg/dl to 15 (4,33) mg/dl) versus the Low Fat group (from 51 (17,96) mg/dl to 21 (13,69) mg/dl (p=0.031)). The Low Carb group demonstrated a trend toward a greater decrease in small dense LDL particle concentration (from 0 (0,53) mg/dl to 0 (0,8) mg/dl) versus the Low Fat group (from 10 (0,83) mg/dl to 0 (0, 60) mg/dl (p=0.13)). Subjects in the Low Carb group also demonstrated a trend toward a greater increase in the concentration of large HDL particles in the Low Carb group (increasing from 12 (7,18) mg/dl to 14 (11,22) mg/dl) versus the Low Fat group (from 10 (7,16) mg/dl to 12 (8,18) mg/dl (p=0.06)).

Conclusions: Subjects with severe obesity and a high prevalence of diabetes or metabolic syndrome demonstrate a shift to a more favorable lipid subfraction profile after 6 months on a carbohydrate-restricted diet compared to a calorie- and fat-restricted diet.